General

Guideline Title

Preexposure prophylaxis for the prevention of HIV Infection in the United States - 2014.

Bibliographic Source(s)

Centers for Disease Control and Prevention (CDC). Preexposure prophylaxis for the prevention of HIV infection in the United States - 2014. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2014. 67 p. [129 references]

Guideline Status

This is the current release of the guideline.

This guideline updates previous versions:

Centers for Disease Control and Prevention (CDC). Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. MMWR Morb Mortal Wkly Rep. 2012 Aug 10;61(31):586-9. [11 references]

Centers for Disease Control and Prevention (CDC). Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. MMWR Morb Mortal Wkly Rep. 2011 Jan 28;60(3):65-8. [10 references]

Recommendations

Major Recommendations

The quality of evidence supporting the recommendations (I-III) and the strength of recommendations (A-C) are defined at the end of the "Major Recommendations" field.

The original guideline document provides comprehensive information for the use of daily oral antiretroviral preexposure prophylaxis (PrEP) to reduce the risk of acquiring human immunodeficiency virus (HIV) infection in adults. The key messages of the guideline are as follows:

- Daily oral PrEP with the fixed-dose combination of tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg has been shown to be safe and effective in reducing the risk of sexual HIV acquisition in adults; therefore,
  - PrEP is recommended as one prevention option for sexually-active adult MSM (men who have sex with men) at substantial risk of HIV acquisition. (IA)
  - PrEP is recommended as one prevention option for adult heterosexually active men and women who are at substantial risk of HIV acquisition. (IA)
  - PrEP is recommended as one prevention option for adult injection drug users (IDU) at substantial risk of HIV acquisition. (IA)
  - PrEP should be discussed with heterosexually-active women and men whose partners are known to have HIV infection (i.e., HIV-

discordant couples) as one of several options to protect the uninfected partner during conception and pregnancy so that an informed decision can be made in awareness of what is known and unknown about benefits and risks of PrEP for mother and fetus. (IIB)

- Currently the data on the efficacy and safety of PrEP for adolescents are insufficient. Therefore, the risks and benefits of PrEP for adolescents should be weighed carefully in the context of local laws and regulations about autonomy in health care decision-making by minors. (IIIB)
- Acute and chronic HIV infection must be excluded by symptom history and HIV testing immediately before PrEP is prescribed. (IA)
- The only medication regimen approved by the U.S. Food and Drug Administration (FDA) and recommended for PrEP with all the populations specified in this guideline is daily TDF 300 mg co-formulated with FTC 200 mg (Truvada). (IA)
    - TDF alone has shown substantial efficacy and safety in trials with IDUs and heterosexually active adults and can be considered as an alternative regimen for these populations, but not for MSM, among whom its efficacy has not been studied. (IC)
    - The use of other antiretroviral medications for PrEP, either in place of or in addition to TDF/FTC (or TDF) is not recommended. (IIIA)
    - The prescription of oral PrEP for coitally-timed or other noncontinuous daily use is not recommended. (IIIA)
- HIV infection should be assessed at least every 3 months while patients are taking PrEP so that those with incident infection do not continue taking it. The 2-drug regimen of TDF/FTC is inadequate therapy for established HIV infection, and its use may engender resistance to either or both drugs. (IA)
- Renal function should be assessed at baseline and monitored at least every 6 months while patients are taking PrEP so that those in whom renal failure is developing do not continue to take it. (IIIA)
- When PrEP is prescribed, clinicians should provide access, directly or by facilitated referral, to proven effective risk-reduction services. Because high medication adherence is critical to PrEP efficacy but was not uniformly achieved by trial participants, patients should be encouraged and enabled to use PrEP in combination with other effective prevention methods. (IIIA)

Definitions:

Quality of Evidence Supporting a Recommendation

I. One or more well-executed randomized, controlled trials with clinical outcomes, validated laboratory endpoints, or both
II. One or more well-executed, nonrandomized trials or observational cohort studies with clinical outcomes
III. Expert opinion

Strength of Recommendation

A. Strong recommendation for the statement
B. Moderate recommendation for the statement
C. Optional recommendation for the statement

Clinical Algorithm(s)

An algorithm titled "Documenting HIV Status" is provided in the original guideline document.

Scope

Disease/Condition(s)

Human immunodeficiency virus (HIV) infection

Guideline Category

Counseling

Prevention

Risk Assessment

Clinical Specialty

Family Practice

Infectious Diseases

Internal Medicine

Pharmacology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Health Care Providers

Pharmacists

Physician Assistants

Physicians

Public Health Departments

Substance Use Disorders Treatment Providers

Guideline Objective(s)

To provide comprehensive clinical practice guideline for the use of preexposure prophylaxis (PrEP) for the prevention of human immunodeficiency virus (HIV) infection in the United States

Target Population

Adult men who have sex with men (MSM), heterosexually active adults, and injection drug users (IDU)

Interventions and Practices Considered

1. Daily oral preexposure prophylaxis (PrEP) with the fixed-dose combination of tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg
2. Weighing risks and benefits of PrEP for adolescents
3. Symptom history and human immunodeficiency virus (HIV) testing immediately before PrEP (to rule out acute and chronic HIV infection)
4. Assessment for HIV infection every 3 months
5. Monitoring of renal function
6. Providing patients access to proven effective risk-reduction services

Major Outcomes Considered

- Risk for human immunodeficiency virus (HIV) acquisition for heterosexually active men and women
- Risk for HIV acquisition in adult injection drug users
- Risk for HIV acquisition in heterosexually active women and men whose partners are known to have HIV infection as one of several options to protect the uninfected partner during conception and pregnancy so that informed decision can be made
- Rate of acquisition of HIV infection among uninfected but exposed men who have sex with men (MSM)
- Preexposure prophylaxis (PrEP) in adolescents

- Safety and effectiveness of PrEP
- Medication adherence
- HIV-infection status during PrEP (i.e., resistance)
- Renal function

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The evidence base for these recommendations is derived from a systematic search and review of published literature. To identify all preexposure prophylaxis (PrEP) safety and efficacy trials pertaining to the prevention of sexual and injection acquisition of human immunodeficiency virus (HIV), a search of the clinical trials registry (http://www.clinicaltrials.gov) was performed by using combinations search terms (preexposure prophylaxis, pre-exposure prophylaxis, PrEP, HIV, Truvada, tenofovir, and antiretroviral). In addition, the same search terms were used to search conference abstracts for major HIV conferences (e.g., International AIDS Conference, Conference on Retroviruses and Opportunistic Infections) for the years 2009 to 2013. These same search terms were used to search PubMed and Web of Science databases for the years 2006 to 2013. Finally, a review of references from published PrEP trial data and the data summary prepared by the U.S. Food and Drug Administration (FDA) for its approval decision confirmed that no additional trial results were available.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence Supporting a Recommendation

I. One or more well-executed randomized, controlled trials with clinical outcomes, validated laboratory endpoints, or both
II. One or more well-executed, nonrandomized trials or observational cohort studies with clinical outcomes
III. Expert opinion

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

In 2009, in recognition of the lead time needed to develop clinical guidance for the safe and effective use of preexposure prophylaxis (PrEP) should clinical trials results support it, the Centers for Disease Control and Prevention (CDC) initiated a formal guidelines development process to allow for early review of the relevant literature, discussion of potential guidelines content given scenarios of potential trial results, and fostering the development of expert and stakeholder consensus. This process was designed to provide a basis for the rapid issuance of interim guidance, to be followed by Public Health Service guidelines as soon as the earliest trial findings indicated sufficient PrEP efficacy and safety to merit its implementation for human immunodeficiency virus (HIV) prevention through one or more routes of transmission.

This guidelines development process was based on a review of experience with the development of other clinical and nonclinical guidelines at the CDC, including those for sexually transmitted disease (STD) treatment and antiretroviral prevention of mother-to-child transmission following the ACTG 076 trial results.

There were five basic components to the process for developing PrEP guidelines:

1. A U.S. Department of Health and Human Services (HHS) Public Health Service (PHS) Working Group to develop interagency consensus on major points of implementation policy and provide agency review of guidelines. This working group included representatives from agencies that would formally clear PHS guidelines (U.S. Food and Drug Administration [FDA], Health Resources and Services Administration [HRSA], National Institutes of Health [NIH], HHS/Office of HIV/AIDS Policy [OHAP]) as well as agencies that may implement such guidance (Indian Health Service [IHS], Veterans Administration [VA]).
2. A CDC writing team responsible for preparing draft guidance documents based on the recommendations of the other groups involved in the guidelines process
3. A number of external work groups responsible for considering specific sets of issues for the planned guidance. Each work group was composed of 5 to 8 members representative of the following:
    - Members of the academic community and scientists with expertise in the content area to ensure that the guideline elements are science-based
    - Health department and clinical users of the guidelines to ensure the feasibility of implementing guideline elements in local and state HIV prevention programs
    - At least one advocate or community-based organization member with personal or professional experience in the content area to serve as an ongoing bridge to community discussions and to supplement the advocate input received by other activities.
    - Geographic diversity (multiple U.S. regions and small/medium/large jurisdictions)
    - Experience with PrEP issues when possible

    External work groups were convened to consider the following areas:

    - Clinical care guidance
    - Clinic-based counseling guidance
    - Integrating PrEP with other prevention services
    - Persons potentially exposed by injection drug use
    - Men who have sex with men (MSM)
    - Women
    - African American, Hispanic/Latino, and other heterosexual men
    - Adolescents

    In addition to these standing work groups, technical expert panels were convened to inform guidelines for PrEP use in the following areas:

    - Public health and clinical ethics
    - Monitoring and evaluation framework
    - Financing and reimbursement issues
    - Preconception and intrapartum use of PrEP
    - Public health legal and regulatory issues

- Issues relevant to benefits managers and insurers

4. A series of stakeholder web/phone conferences were held to receive input on questions, concerns, and preferences from a variety of perspectives including those of community-based organizations, state and local acquired immunodeficiency syndrome (AIDS) offices, professional associations, and others.
5. After the publication of the first efficacy trial results, a face-to-face consultation of external experts, partners, agencies, and other stakeholders was held to consider the recommendations for guidance made by the above groups and to discuss any additional ideas for inclusion in PrEP guidelines.

This process allowed wide input, transparency in discussing the many issues involved, time for the evolution of awareness of PrEP and ideas for its possible implementation, in addition to facilitating the development of a consensus base for the eventual guidance. At the same time, it allowed for guidelines based on expert opinion, and recommendations deemed feasible by clinical providers and policymakers.

On the basis of results from the first 4 activities listed above and the publication in late November 2010 of results from the first clinical trial to show substantial efficacy and safety, the CDC issued interim guidance for PrEP use among men who have sex with men in January 2011. This interim guidance was followed by a face-to-face meeting of external in May 2011. As efficacy and safety results were published, additional interim guidance documents were issued for heterosexually active adults (August 2012) and injection drug users (July 2013).

A draft guidelines document incorporated recommendations from participants in the development process and information gleaned from literature reviews, including PrEP clinical trial results. The draft also addressed guidelines standards for review of the strength of evidence (Grading of Recommendations Assessment, Development and Evaluation [GRADE] approach) as well as a format designed to promote guideline implementation (Guideline Implementability Appraisal [GLIA]), dissemination (Global Evaluation and Monitoring [GEM]), and adoption (Appraisal of Guidelines for Research and Evaluation [AGREE]).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

A. Strong recommendation for the statement
B. Moderate recommendation for the statement
C. Optional recommendation for the statement

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The draft clinical practice guideline and providers supplement were reviewed by the Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), Health Resources and Services Administration (HRSA), and the U.S. Department of Health and Human Services (HHS), and a series of webinars were held in 2012 and 2013 to obtain additional expert opinion and public engagement on draft recommendations for preexposure prophylaxis (PrEP) use. The draft guideline and supplement were then reviewed by a panel of 6 external peer reviewers who had not been involved in their development. At each step, revisions were made in response to reviewer and public comments received.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of preexposure prophylaxis (PrEP) in reducing human immunodeficiency virus (HIV) acquisition, appropriate regular monitoring of HIV status, and ongoing risk-reduction and PrEP medication adherence counseling

Potential Harms

- All patients whose sexual or drug injection history indicates consideration of preexposure prophylaxis (PrEP) and who are interested in taking PrEP must undergo laboratory testing to identify those for whom this intervention would be harmful or for whom it would present specific health risks that would require close monitoring.
- In multivariable analyses, back pain was the only adverse event associated with receipt of tenofovir disoproxil fumarate (TDF).
- In one study of daily oral TDF/emtricitabine (FTC) or TDF modest increases in gastrointestinal symptoms and fatigue were reported in the antiretroviral medication groups compared with the placebo group, primarily in the first month of use.
- In another study of the human immunodeficiency virus (HIV) prevention efficacy and clinical safety of daily TDF/FTC among heterosexual women in South Africa, Kenya, and Tanzania, only nausea and vomiting (in the first month) and transient, modest elevations in liver function test values were the adverse events more common among those assigned to TDF/FTC than those assigned to placebo. In another study the rates of nausea and vomiting were higher among TDF than among placebo recipients in the first 2 months of medication but not thereafter.
- Decreases in bone mineral density (BMD) have been observed in HIV-infected persons treated with combination antiretroviral therapy (including TDF-containing regimes). Any person being considered for PrEP who has a history of pathologic or fragility bone fractures or who has significant risk factors for osteoporosis should be referred for appropriate consultation and management.
- PrEP use periconception and during pregnancy by the uninfected partner may offer an additional tool to reduce the risk of sexual HIV acquisition. Both the U.S. Food and Drug Administration (FDA) labeling information and the perinatal antiretroviral treatment guidelines permit this use. However, data directly related to the safety of PrEP use for a developing fetus are limited. Providers should discuss available information about potential risks and benefits of beginning or continuing PrEP during pregnancy so that an informed decision can be made.
- The safety of PrEP with TDF/FTC or TDF alone for infants exposed during lactation has not been adequately studied. However, data from studies of infants born to HIV-infected mothers and exposed to TDF or FTC through breast milk suggest limited drug exposure. Additionally, the World Health Organization has recommended the use of TDF/FTC or 3TC/efavirenz for all pregnant and breastfeeding women for the prevention of perinatal and postpartum mother-to-child transmission of HIV. Therefore, providers should discuss current evidence about the potential risks and benefits of beginning or continuing PrEP during breastfeeding so that an informed decision can be made.
- TDF presents a very high barrier to the development of hepatitis B virus (HBV) resistance. However, it is important to reinforce the need for consistent adherence to the daily doses of TDF/FTC to prevent reactivation of HBV infection with the attendant risk of hepatic injury, and to minimize the possible risk of developing TDF-resistant HBV infection.

Qualifying Statements

Qualifying Statements

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Centers for Disease Control and Prevention (CDC). Preexposure prophylaxis for the prevention of HIV infection in the United States - 2014. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2014. 67 p. [129 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Jan 28 (revised 2014)

Guideline Developer(s)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

Source(s) of Funding

United States Government

Guideline Committee

Centers for Disease Control and Prevention (CDC) Preexposure Prophylaxis (PrEP) Guidelines Writing Team

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

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This guideline updates previous versions:

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Centers for Disease Control and Prevention (CDC). Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. MMWR Morb Mortal Wkly Rep. 2011 Jan 28;60(3):65-8. [10 references]

Guideline Availability

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site .

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

Availability of Companion Documents

The following are available:

- Preexposure prophylaxis for the prevention of HIV infection – 2014: clinical providers' supplement. Atlanta (GA): Centers for Disease Control and Prevention; 2014. 43 p. Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site .
- PrEP: a new tool for HIV prevention. CDC fact sheet. Atlanta (GA): Centers for Disease Control and Prevention; 2013 Jun. 4 p. Electronic copies: Available from the CDC Web site .
- Pre-exposure prophylaxis (PrEP) for HIV prevention. CDC fact sheet. Atlanta (GA): Centers for Disease Control and Prevention; 2014 May. 2 p. Electronic copies: Available from the CDC Web site .

- Provider information sheet: PrEP during conception, pregnancy, and breastfeeding. Information for clinicians counseling patients about PrEP use during conception, pregnancy, and breastfeeding. Atlanta (GA): Centers for Disease Control and Prevention; 2014. 4 p. Electronic copies: Available from the CDC Web site . Also available in Spanish .
- Pre-exposure prophylaxis (PrEP). Prevention research web resource. Electronic copies: Available from the CDC Web site .

Patient Resources

The following are available:

- Patient information sheet: acute HIV infection. Information about acute HIV infection and PrEP. Atlanta (GA): Centers for Disease Control and Prevention; 2014. 2 p. Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site . Also available in Spanish .
- PrEP information sheet: pre-exposure prophylaxis (PrEP) for HIV prevention. Frequently asked questions. Atlanta (GA): Centers for Disease Control and Prevention; 2014. 2 p. Electronic copies: Available from the CDC Web site . Also available in Spanish .
- Truvada medication information sheet: Truvada medication information sheet for patients. Atlanta (GA): Centers for Disease Control and Prevention; 2014. 2 p. Electronic copies: Available from the CDC Web site . Also available in Spanish .
- PrEP 101. Patient web resource. Electronic copies: Available from the CDC Web site .
- CDC features: PrEP for HIV prevention. Web resource. Electronic copies: Available from the CDC Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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